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REVIEW ARTICLE

Sublingual Immunotherapy in Children: An Updated Review

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Although pharmacological therapy and allergen avoidance are effective means of managing allergic disease, allergen-specific immunotherapy is able to treat not only the symptoms, but also the underlying causes of the disease. Sublingual immunotherapy (SLIT) has been shown to be effective in patients with allergic diseases. It has demonstrated long-term clinical benefits and shown the potential to modify the course of allergic disease in children with rhinitis, conjunctivitis, and asthma. The precise mechanisms of SLIT remain unclear, but antigen-presenting cells in the oral mucosa may induce regulatory T-cells that suppress the allergic immune response by increasing production of interleukin-10. SLIT has also been shown to increase allergen-specific IgG antibodies that antagonize and block the allergic response. SLIT was well tolerated in all reported, double-blinded, placebo-controlled, randomized trials. SLIT is an ideal means of treating the pediatric population because of its excellent safety and good compliance. However, the optimal dose and duration of SLIT require further investigation.

1. Introduction

The prevalence of IgE-mediated hypersensitivity has increased over the past few decades. Related clinical diseases range from trivial rhinitis to life-threatening asthma.[1] Although pharmacological therapy and allergen avoidance are effective means of managing allergic disease, allergen-specific immunotherapy is able to treat not only the symptoms, but also the underlying causes of the disease.[2] An early study in 1961 reported the use of subcutaneous immunotherapy (SCIT) in children,[3] but subsequent studies found that this administration route was associated with the risk of severe adverse events. Safer routes of administration have therefore been investigated and developed. Oral and bronchial administration have been abandoned because controlled trials failed to demonstrate clinical efficacy and safety. Local nasal immunotherapy, although effective and safe, is limited because it requires a particular administration technique, and is only effective against rhinitis.[4] Sublingual immunotherapy (SLIT) is considered to be a better treatment modality associated with less severe systemic adverse effects and better compliance, compared with conventional SCIT.

In 1993, the European Academy of Allergy and Clinical Immunology proposed that the safety and

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efficacy of SLIT should be investigated. In 1998, the World Health Organization suggested that SLIT could be used in adults with allergic rhinitis, but decided that there was still insufficient evidence to justify its use in children. In 2001, an Allergic Rhinitis and its Impact on Asthma (ARIA) document reported that SLIT had been evaluated in studies of allergic rhinitis induced by certain pollens and mites. In 2003, the American Academy of Allergy, Asthma & Immunology (AAAAI)-American College of Allergy, Asthma and Immunology (ACAAI) clinical guidelines concluded that "further studies are needed to confirm the efficacy and safety of optimal dose sublingual-swallow immunotherapy in children and adults". The AAAAI and ACAAI formed a joint task force with the purpose of providing a comprehensive, updated report on SLIT for the North American allergy community. There have been two studies of SLIT in Taiwan. A multi-center, double-blind, randomized and placebo-controlled study by Niu et al[5] showed that SLIT administered at ultra-high doses in a rushed schedule to mite-sensitive asthmatic children improved asthma scores and lung function tests. Another double-blind, randomized and placebo-controlled study by Leu et al[6] also revealed that SLIT was clinically effective in reducing symptoms and medication use in asthmatic children sensitized to mites. Mite-specific IgG4 significantly increased after treatment with SLIT in this study. Both these SLIT studies in Taiwan demonstrated good patient tolerance and safety. This review explores the efficacy, mechanisms, safety, compliance, and recent advances in SLIT for the treatment of children.

2. Efficacy of SLIT in Children

The results of many double-blind, placebo-controlled, randomized trials of SLIT treatment in children, using a wide range of allergen doses, have been published (Table 1). The use of SLIT for the treatment of allergic rhinitis caused by mites, or by grass, birch, or *Parietaria* pollen, was examined in a meta-analysis including 22 trials and 979 patients, which showed significant efficacy compared with placebo.[7] However, studies in this meta-analysis that only involved children with allergic rhinitis showed no significant reduction in symptoms or medication scores. However, it may not be possible to reach a reliable conclusion based on these studies because of the small numbers of participants; there were only five studies involving 218 children.[7] Another meta-analysis of the use of SLIT to treat pediatric patients with allergic rhinitis included 10 studies and 577 patients, and demonstrated the efficacy of SLIT by reductions in symptoms and medication use after immunotherapy. It also showed that SLIT administered for more than 18 months using pollen extracts was more effective than SLIT courses administered for less than 18 months and using mites.[8]

There have been fewer studies of SLIT for asthma treatment than for the treatment of allergic rhinitis, and the effects of SLIT on asthma remain controversial. A meta-analysis of SLIT for asthma, including 25 studies and 1,706 patients, revealed a significant reduction in asthma severity based on the use of asthma medications, lung function, and bronchial provocation, but did not show improvements

Table 1 Double-blind, placebo-controlled trials of the efficacy of sublingual immunotherapy for the treatment of children since 2000

First author	Year	Reference	Age range (yr)	No. of patients Active/Placebo	Allergen	Duration	Disease	Effects
Caffarelli	2000	41	4–14	24/20	Grass	3 mo	R/A	+
Pajno	2000	32	8–15	12/12	Mite	2 yr	A	+
Bahceciler	2001	42	7–15	8/7	Mite	6 mo	R/A	+
Ippoliti	2003	43	5–12	47/39	Mite	6 mo	R/A	+
Marcucci	2003	44	4–16	13/11	Mite	1 yr	R/C/A	+
Pajno	2003	14	8–14	15/15	*Parietaria*	13 mo	R/C/A	+
Wuthrich	2003	45	6–13	11/11	Grass	2 yr	R/A	+
Bufe	2004	46	6–13	68/74	Grass	3 yr	R/A	+
Novembre	2004	17	5–14	48/49	Grass	3 yr	R/A	+
Rolinck-Werninghaus	2004	47	3–14	39/38	Grass	3 yr	R/C	+
Niu	2006	5	6–12	49/48	Mite	6 mo	A	+
Lue	2006	6	6–12	10/10	Mite	6 mo	A	+
Valovirta	2006	48	6–14	59/29	Mixture	18 mo	R/C	+
Ibanez	2007	10	5–12	45/15	Grass	1 mo	R/C/A	+
Pham-Thi	2007	13	5–15	55/56	Mite	18 mo	A	–

R = rhinitis; C = conjucntivitis; A = asthma.

in asthma symptoms.[9] More recent studies have demonstrated the efficacy and safety of SLIT in children with grass pollen seasonal allergic rhinoconjunctivitis and asthma.[10] One study also found that SLIT produced a greater reduction in allergic symptoms and airway inflammation in children with asthma who were allergic to house dust mites compared with pharmacotherapy.[11] SLIT also improved subjects' forced vital capacity, forced expiratory volume in first second, and peak expiratory flow, as compared with baseline, in mite-sensitive asthmatic children.[5] As an adjunct to pharmacotherapy, 3 years of SLIT combined with pharmacotherapy resulted in reductions in both the duration and dose of inhaled corticosteroids and allowed the successful discontinuation of inhaled corticosteroids, along with improvements in lung functions.[12] Nonetheless, Pham-Thi et al demonstrated that although SLIT resulted in a significant reduction in the allergic response to house dust mites by reducing skin sensitivity as well as specific IgE and IgG antibodies, it did not provide any additional benefit in children with mild-moderate asthma who were already optimally controlled by pharmacotherapy and mite avoidance.[13] Pajno et al also reported that SLIT had no additional benefit in seasonal asthmatic children allergic to *Parietaria* pollen who had been treated with inhaled fluticasone propionate, although SLIT could reduce the early and late skin responses and significantly improve the non-bronchial symptoms.[14]

Allergic rhinitis, conjunctivitis and asthma are considered to be different manifestations of atopy. Immunotherapy for allergic rhinitis may prevent the development of asthma. Over the years, increasing amounts of evidence have shown that SCIT can prevent the progression of rhinitis to asthma, and can reduce the severity of asthma.[15] A 10-year follow-up study recently showed that a 3-year course of SCIT produced long-term clinical effects and had the potential to prevent the development of seasonal and perennial asthma in children.[16] Regarding SLIT, a study of children with rhinoconjuctivitis demonstrated that after 3 years of co-seasonal SLIT therapy with grass pollen allergen, symptoms of seasonal allergic rhinitis and the development of seasonal asthma were reduced.[17] In addition to its ability to modify the natural history of allergic disease and prevent the onset of new sensitization, immunotherapy also maintains its clinical efficacy 3–5 years after its discontinuation.[18] In children with asthma due to house dust mites, SLIT reduced the incidence of asthma at the end of treatment, and continued to have an effect even 4–5 years after treatment discontinuation.[19] The clinical improvement was strengthened by the use of long-term (2–3 years) SLIT.[20]

3. Mechanisms of SLIT

Most studies of SLIT have examined its efficacy and safety. However, the exact mechanisms behind SLIT are still under investigation. Contact of the allergen with the oral mucosa is a key to the success of SLIT. A systemic immune response, as well as a local immune reaction, is involved. The Langerhans-like dendritic cells capture the allergen in the oral cavity. They subsequently mature and migrate to the proximal lymph nodes, where blocking IgG antibodies are produced and suppressor T lymphocytes are induced.[21] A specific function for these cells has been suggested because of their high expression of Fcε receptor type I, major histocompatibility complex class I and II, and some costimulatory molecules (CD40, CD80/B7.1, and CD86/B7.2), which profoundly differ from those of skin Langerhans cells.[22]

An increase in IgG production is one mechanism of immunotherapy. Antigen-specific IgG antibodies can antagonize and block the allergic response resulting from the production of IgE against the harmless antigen. The balance between IgE and IgG, especially IgG4 subtype, is crucial for the success of allergen-specific immunotherapy. SLIT has been shown to increase allergen-specific IgG4 levels in children with asthma due to house dust mites,[23] and with allergic rhinitis,[24] and these findings were further confirmed in a meta-analysis of SLIT studies.[7] A decrease in the IgE/IgG4 ratio has been observed in several SLIT studies in children with asthma caused by house dust mites[25] and with allergic rhinitis,[24] though a recent study reported a lack of detectable alteration in immune response.[26] Further studies are needed to clarify the mechanism of blocking antibodies in SLIT.

Allergic patients are known to usually mount strong allergen-specific T-cell responses involving T helper 2 (Th2) cells.[27] In healthy individuals, regulatory T cells represent the dominant allergen-specific subset (Figure 1). Regulatory T cells secrete interleukin (IL)-10 (type 1 regulatory T cells; Tr1) and transforming growth factor (TGF)-β (Th3 cells), which directly or indirectly suppress allergic inflammation. The purpose of allergen-specific immunotherapy is to restore tolerance by shifting T-cell responses from Th2- to regulatory T-cell responses. Studies have shown that SCIT can induced regulatory T cells to downregulate both Th1 and Th2 responses.[28] To date, however, there is less evidence regarding the impact of SLIT on T-cell responses. SLIT failed to induce the proliferation of dendritic cells or T lymphocytes in the epithelium or lamina propria of the oral mucosa in children with rhinoconjunctivitis and asthma due to olive pollen.[29] SLIT had no significant effect on T-cell functions, such as cytokine production, in children with seasonal

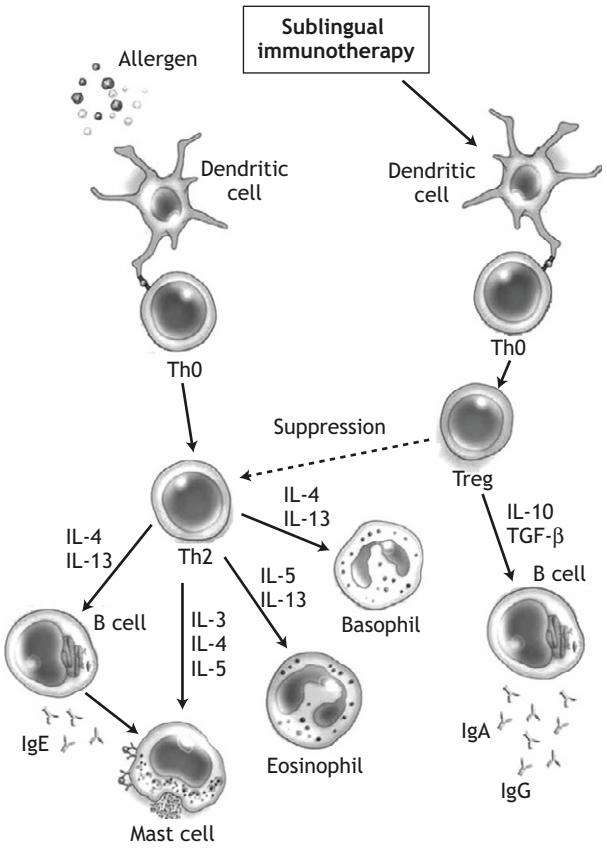

Figure 1 Possible mechanism of sublingual immunotherapy (SLIT). SLIT deals with allergy by inducing long-term immune deviation towards regulatory T cells responses. During an allergic immune response, Th2 cells produce interleukins that promote IgE production by B cells, and activate mast cells, eosinophils and basophils that release inflammatory mediators. Regulatory T cells suppress the activity of Th2 cells and promote IgG and IgA production, rather than IgE. The main cytokines involved appear to be interleukin-10 and transforming growth factor-β. IL-10=interleukin-10; TGF-β=transforming growth factor-β.

allergic rhinoconjunctivitis to grass pollen.[26] A recent preliminary study showed that IL-10 increased *in vitro* stimulation by *Dermatophagoides*, as well as recall antigens from *Candida albicans* and phytohaemagglutinin, in peripheral blood mononuclear cells from house dust mite-allergic patients after 3 years of SLIT.[30] T-cell proliferation induced *in vitro* by *C. albicans*, *Parietaria*, and grasses was significantly reduced in patients treated with SLIT for house dust mite allergy.[31] Further investigations are needed to confirm the roles of regulatory T cells, IL-10, and TGF-β in patients treated with SLIT.

4. Dosing, Frequency and Duration of SLIT

Published controlled trials of SLIT have used variable doses of allergens. Compared with SCIT, SLIT requires 50–100 times more allergen to reach similar levels of efficacy.[2] However, it has been suggested that the use of cumulative doses up to a threshold is important for successful SLIT, and these may not differ greatly from the doses used in SCIT.[32] SLIT may be started at the full maintenance dose, without the gradual increase in dose that is usual for SCIT. The only agent that is currently commercially available for SLIT is extract of grass pollen, and the standard dose consists of a single sublingual tablet, taken once daily. Treatment is most effective when initiated at least 2 months before the start of the pollen season.[33] Studies of SLIT in children have used variable cumulative doses measured in different units. The duration ranged from 3 months to 3 years. To date, there are no experimental data on the optimal duration of SLIT, and the optimal maintenance dose and administration schedule require further investigation.

5. Safety and Compliance of SLIT

The excellent safety of allergens administrated by the sublingual route, as shown by numerous studies in past years, makes SLIT a suitable method for treating allergies in the pediatric population.[34] SCIT induced more systemic and anaphylactic reactions in children with asthma than in children with rhinitis, and the severity differed between different allergens.[35] These disadvantages of the subcutaneous route confine the use of SCIT to specialized medical centers. By contrast, all reported, double-blind, placebo-controlled, randomized trials of SLIT have shown it to be well tolerated. SLIT has been used in both rhinitis and asthma patients, with no occurrence of anaphylactic reactions,[23,36] and its safety has also been confirmed in clinical trials in children with rhinitis and asthma.[36] The most frequent adverse effects were local (oral pruritus, throat irritation or mouth edema) or gastrointestinal (nausea, vomiting, diarrhea or abdominal pain). The overall incidence of side effects varied from 3–18% of patients.[19] In a recent extensive review of the literature, 17 serious adverse events, mainly asthma, and two anaphylactic events, were reported.[37] No life-threatening or fatal events have been reported in any study.

Compliance with SLIT is generally good, and only a small number of patients have been withdrawn because of worsening symptoms. In the pediatric population using SLIT, incidents of poor compliance were mostly due to parents who discontinued the treatment because the symptoms had improved.[17] Compliance is an important factor for increasing the efficacy and decreasing the occurrence of side effects.[38] Therefore, educational and socioeconomic

status should be taken into consideration when administering SLIT.

6. Future Developments in SLIT

In the majority of cases, SLIT is administered in the form of drops, with only occasional use of tablets.[7] The change from drops to tablets could provide a further advance in standardizing SLIT dosing and vaccine development. The convenience of taking tablets may enhance compliance, which is a key to increasing efficacy and reducing side effects.

Sublingual vaccines are currently based on aqueous biological extracts from natural allergen sources, and have demonstrated both safety and clinical efficacy. With recent advances in the understanding of oral mucosal immunity and new proteomic techniques, second-generation sublingual vaccines based on recombinant allergens are under development. These recombinant allergens are molecularly defined, and are easier and more reproducible and traceable to produce. The strategy of using recombinant allergens represents an alternative approach directed at eliciting an IgG response and activating T cells, while reducing the capacity to bind allergen-specific IgE, thereby reducing the risk of IgE-dependent side effects such as mast cell degranulation.[39] Tests of SCIT using subcutaneous recombinant vaccines have yielded promising results.[40] However, there have been no clinical trials of recombinant allergen sublingual vaccines. The use of recombinant allergens may permit an individualized approach to diagnosis and therapy in the future.

Vaccine preparation strategies also consider the use of biological or synthetic adjuvants to improve allergen presentation, and new allergen formulations other than drops or tablets (e.g., powder, biofilms or mucoadhesive tablets) to prolong mucosal contact and facilitate allergen capture by immune cells. These approaches could help to enhance SLIT efficacy, reduce allergen dosage, and simplify administration schedules.

7. Conclusions

The use of SLIT provides an attractive option, especially in the pediatric population, for outpatient, home-based and self-administered therapy. It is preferable to the use of SCIT, which is limited to medical centers and must be administered by health care professionals. Good compliance with SLIT may result in better chances of success for immunotherapy. The long-term clinical efficacy of SLIT has been demonstrated in children with allergic rhinitis and asthma, and the progression of atopy was reduced. SLIT is particularly appropriate for children because of its safety, tolerable adverse effects, and good compliance. Although the exact immunological mechanisms by which SLIT induces tolerance against allergens remain unclear, current understanding, particularly of the role of regulatory T cells, may enable the development of improved treatment strategies. Various forms of sublingual vaccine involving the use of adjuvants, new allergen formulations, and recombinant allergens, are currently under evaluation. Advances in these fields can provide information leading to more rational and safer approaches to doses and optimal duration in order to achieve the best long-term effects that could, in the future, prevent and cure allergic disease.

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